REMARKS

Claims 1, 2, 4, and 12-15 are under examination in the present case. Each of these claims is rejected under 35 U.S.C. § 112, first paragraph, and claims 1-4 are rejected under 35 U.S.C. § 102(b). The rejections are addressed below.

Support for the Amendments

Support for the claim amendments is found throughout the specification. For example, support for the amendment of claim 1 and for new claim 17, which recite methods for identifying candidate compounds that ameliorate or delay an impaired glucose tolerance condition, atherosclerosis, or obesity, is found at original claim 2. Further support for the amendment of claim 1 which recites 85% amino acid sequence identity to SEQ ID NO: 54, is found at page 26, lines 26 and 27; support for the amendments of claim 12 and for new claim 16, which recite 90% and 95% amino acid sequence identity to SEQ ID NO: 54, respectively, is found, for example, at page 20, lines 5-8. Support for the limitation of claim 1 and new claim 17 that requires that the gene used in the methods functions in insulin signaling is found, for example, at page 54, lines 1 and 2. Support for the limitation of new claim 17 which recites "hybridizes under stringent conditions" is found at page 78, second paragraph, to page 79. Support for new claims 18-20 is found in original claims 12-15.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 1, 2, 4, and 12-15, which feature compound screening methods involving polypeptides encoded by *daf-16*-related nucleic acids, are rejected under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description on the grounds that the *daf-16* gene is not defined by structural or functional limitations. As applied to the present claims, this rejection should be withdrawn.

Present claim 1, and its dependent claims, now require a nucleic acid "having at least 85% amino acid sequence identity to SEQ ID NO:54" and that "functions in insulin signaling." Applicants note that new claim 17, and its dependent claims, are directed to compound screening methods that also require a nucleic acid that hybridizes to SEQ ID NO:54 under stringent conditions and that functions in insulin signaling.

Given that the claims now recite characteristic functional and structural features of DAF-16-related polypeptides, Applicants' claims clearly satisfy the written description requirement (M.P.E.P. 2163 II A 3ii):

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by ...*disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics*, sufficient to show the applicant was in possession of the claimed genus...

In particular, Applicants have disclosed, in their specification, identifying characteristics of *daf-16*, including functionally important structural features. Using sequence analysis, Applicants have identified DAF-16 as a member of the forkhead family of transcription factors (page 53, lines 25-27), and, at Figure 21A, Applicants provide an alignment of *C. elegans* DAF-16 with other forkhead family members. This alignment shows that human FKHR and AFX polypeptides share regions having a high degree of sequence identity. In particular, DAF-16, FKHR, and AFX share a characteristic structural motif (SEQ ID NO:54) found within the forkhead DNA binding domain (page 75, lines 6-8, and pages 76-77). This structural motif is now a central element of Applicants' claims.

Moreover, Applicants have demonstrated that the structural similarities between the members of the *daf-16* family are echoed in functional relatedness. As stated in Dr. Ruvkun's Declaration, which was submitted with the reply filed on July 24, 2003, paragraph 1, although *C. elegans* and humans are evolutionarily distant organisms, *C. elegans daf-16* and human proteins FKHR and AFX are highly related. In fact, Dr. Ruvkun and his colleagues have shown that FKHR and DAF-16 are so closely related that the human protein is able to functionally substitute for *C. elegans* DAF-16 *in vivo*.

While the Office asserts that the claimed invention encompasses DAF-16 variants that might not share the functional characteristics of DAF-16, given that the human protein is able to functionally substitute for the *C. elegans* polypeptide, one skilled in the

art would understand that DAF-16 proteins having at least 85% amino acid sequence identity to SEQ ID NO:54 would also function in insulin signaling and are appropriately included in Applicants' screening claims.

In view of the above, the written description rejection should be withdrawn. Applicants have shown that *C. elegans daf-16*, human AFX, and human FKHR are representative of DAF-16 proteins generally. In addition, Applicants have provided a detailed description of DAF-16, including the nucleic acid and amino acid sequences of *daf-16*, an alignment of DAF-16 and other forkhead family members, and identification of a structurally and a functionally important motif that is characteristic of all members of this family. Moreover, Applicants have shown that *C. elegans* DAF-16, human AFX, and human FKHR as species are clearly representative of the genus, and that members of this family are so closely related as to be capable of functional substitution.

This first basis for the § 112, first paragraph rejection should be withdrawn.

Enablement

Claims 1, 2, 4, and 12-15 are further rejected, under 35 U.S.C. § 112, first paragraph, as lacking enablement, on the grounds that Applicants fail to enable methods for decreasing the expression of all *daf-16* variants. In support of the rejection, the Office asserts that it would require undue experimentation to make and test the function of all claimed *daf-16* variants. As applied to the present claims, this rejection may be

withdrawn These claims are now limited to screening methods that require a polypeptide having at least 85% amino acid sequence identity to SEQ ID NO:54 and that function in insulin signaling.

The proper test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1318 (Fed. Cir. 1985). As detailed below, at the time of filing, a skilled artisan, using no more than routine experimentation and the teachings of the present specification, could easily identify and test the function of nucleic acids falling within Applicants' current claims.

At pages 76 and 77 of the specification, Applicants disclose five amino acid sequences that may be used to identify a *daf-16* family member present in a sequence database or that may be used to design degenerate probes to identify such a gene present in a genomic or cDNA library. Methods for expressing the identified nucleic acids in *daf-16* mutant nematodes and assaying the nematodes for complementation are described at page 79 of Applicants' specification. Applicants have already demonstrated the feasibility of carrying out such methods, as evidenced in the Declaration of Dr. Ruvkun, which was filed on July 24, 2003, previously of record. Dr. Ruvkun and his colleague disclose that a *daf-16* human homolog expressed under the control of the *daf16β* promoter in worms having mutations in *daf-16* and *daf-2* was expressed and was able to

functionally replace the worm protein (Declaration of Dr. Ruvkun, paragraph 3, and Lee et al. Curr. Biol. 11:1950-1957, 2001). In view of the above evidence demonstrating that *daf-16* family members may be identified and readily tested for function, the enablement rejection should be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 1-4 are further rejected under 35 U.S.C. § 102(b) based on the assertion that the claims are anticipated by Gottlieb et al. (Genetics 137:107-120, 1994, hereafter "Gottlieb"). As applied to the present claims, this rejection should be withdrawn.

Claim 1 and its dependent claims are now directed to a method for identifying a candidate modulatory compound that ameliorates or delays an impaired glucose tolerance condition, atherosclerosis, or obesity. These claims cannot be anticipated by Gottlieb, as this reference fails to describe a role for *daf-16* in glucose tolerance, atherosclerosis, or obesity.

The Office asserts that "obesity is a relative term based upon body mass. Therefore the dauer-larvae, which have thin bodies are considered non-obese as compared to fat (obese) L3 worms." The skilled artisan, provided with the teachings of Gottlieb, would not have inferred any role for *daf-16* in regulating obesity. While morphological differences clearly exist between dauer and L3 larvae, these differences cannot correctly be described using terms such as "fat" and "thin."

The morphological differences that exist between L3 and dauer larvae do not parallel the differences that exist between "fat" and "thin" humans. While L3 larvae are plainly larger than dauers, they are not overweight. Similarly, a dauer's "thinness" does not arise from a decrease in body mass, but from an increase in density. As described in the accompanying Exhibit (*C. elegans II*, ed. J. Priess, Chapter 26, section 2, under the heading "Genetic and Environmental Regulation of Dauer Larva Development," http://www.ncbi.nlm.nih.gov/entrez).

> Dauer larvae are easily distinguished from other developmental stages. *They are thin and dense due to shrinkage of the hypodermis at the dauer-specific molt.* They acquire resistance to detergent treatment about 1 hour after radial shrinkage of the body, presumably as a result of cuticle modification and the occlusion of the buccal cavity. (Emphasis added. References removed.)

Given that a dauer's "thinness" arises from the shrinkage of their external cuticle, the skilled artisan would not conclude that the differences that exist between L3 and dauer larvae parallel those that exist between fat and thin humans. Thus, the Office's basis for the § 102 rejection is in error, and this rejection should also be withdrawn.[1]

Information Disclosure Statements

Applicants note that the Forms PTO-1449 that were submitted with Information Disclosure Statements filed on April 27, 2001, March 5, 2002, and March 19, 2003, have

[1] For the record, Applicants also disagree with the Office's assertion that "the cited art teaches. . . construction of worms encoding *daf-16* wild-type or mutated *daf-16* trangenes. . . " In fact, Gottlieb fails to describe *any* transgenic nematode. Gottlieb merely describes the identification of mutant nematodes expressing *endogenous* wild-type and mutant *daf-16* genes.

not been initialed and returned. Applicants hereby request that they be initialed and returned with the next Office action.

CONCLUSION

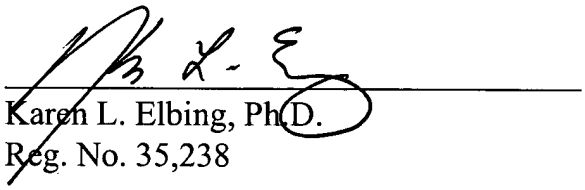
Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the final Office action for one month, to and including March 18, 2004, and a check in payment of the required extension fee.

If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 18 March 2004



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II. The Dauer State

A. Morphology

Dauer larvae are easily distinguished from other developmental stages. They are thin and dense due to shrinkage of the hypodermis at the dauer-specific molt (Cassada and Russell 1975; Albert and Riddle 1988). They acquire resistance to detergent treatment about 1 hour after radial shrinkage of the body (Swanson and Riddle 1981), presumably as a result of cuticle modification and the occlusion of the buccal cavity (Fig. 2) (Cassada and Russell 1975; Popham and Webster 1979; Albert and Riddle 1983, 1988).

Transverse-section electron micrographs of the cuticle show a thickened outer cortex and a dauer-specific, striated inner layer (Cassada and Russell 1975; Popham and Webster 1978; Cox et al. 1981b). The dauer cuticle has lateral ridges (alae) not present on L2, L3, or L4 larvae that are visible with Nomarski optics. A detergent-soluble 37-kD hydrophobic protein exposed on the surface of the dauer larva is not found on other stages (Blaxter 1993a). Many tissues and organs exhibit dauer-specific morphology: Pharyngeal pumping is suppressed (Cassada and Russell 1975) and the isthmus and terminal bulb of the pharynx are constricted (Vowels and Thomas 1992); the lumen of the intestine is shrunken and the microvilli are condensed (Popham and Webster 1979); the excretory gland lacks secretory granules (Nelson et al. 1983); and several sensory neurons exhibit altered position or dendrite orientation (Albert and Riddle 1983).

The anterior sensory ultrastructure of the dauer larva was examined in several specimens and compared with that of the L2 larva (Albert and Riddle 1983). In some instances, comparisons were made with L3, postdauer L4, and adult stages. Whereas sensory morphology in different nondauer stages remains constant, it differs in the dauer larva, providing an example of developmental plasticity in the nervous system (Jorgensen and Rankin, this volume). Dauer-specific sensory modifications in the amphids, inner labial neurons, and the deirids may play a part in dauer-specific behavior.

The amphids are a pair of prominent chemosensory organs located on either side of the head. Each amphid consists of two support cells and 12 neurons, eight of which are exposed to the environment through a pore in the cuticle near the tip of the head (Ward et al. 1975; Ware et al. 1975; Bargmann and Mori, this volume). Dendritic processes extend anteriorly from cell bodies located near the circumpharyngeal nerve ring, and axons extend into the ring. A sheath cell forms